REMARKS

1. Overview of Claim Amendments

Claim 1 has been amended to correct a typographical error.

New claim 84 recites that said purified menthol is menthol in a substantially purer form than menthol in peppermint oil.

New claim 85 recite that the composition does not comprise peppermint oil. Basis is at page 10, lines 19-21, which excludes a plant extract such as peppermint oil:

> Preferably, the pharmaceutical compositions of the invention are essentially free of crude plant extracts or fractions thereof. The compositions may off course comprise fractions mainly consisting of flavonoids or menthol.

Note also that at page 5, line 32, applicants acknowledged that Berg, WO 02/09699 taught use of peppermint oil as a "flagrant" in a flavonoid composition for the treatment of the common cold. Peppermint oil may therefore be properly disclaimed in accordance with *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) and MPEP 2173.05(i), third para.

New claim 86 recites that the composition is essentially free of components of peppermint oil other than menthol, with basis at page 9, lines 20 to 33. and claims 12, 13 and new claim 92 similarly exclude specific named constituents (basis at at page 11, lines 31 to page 12, line 14). At page 9, lines 20-27, applicants teach

> In another embodiment the present invention relates to pharmaceutical compositions comprising one or more flavonoids, wherein said compositions are <u>essentially</u>

> free of any component of peppermint oil, which is not menthol. Preferably, said compositions are free of any components of Japanese peppermint oil. Said compositions may in addition to flavonoids comprise one or more other active ingredients, for examples a metal salt and/or metal complex and/or menthol. The compositions may also comprise flavouring agents other than peppermint oil. [emphasis added]

Exemplary components of peppermint oil are listed at page 9, lines 29-33.

Page 26, lines 20-21 discloses, "said medicament is preferably free of all components of peppermint oil except menthol".

Peppermint oil, and its constituents other than menthol, are also excluded by the teachings at page 11, lines 31 to page 12, line 14:

> In one embodiment it is preferred that the pharmaceutical composition is essentially free of other terpenes than menthol. Hence, the pharmaceutical composition is in this embodiment of the invention preferably essentially free of one or more selected from the group consisting of menthone, menthyl acetate, limonene and neomenthol. More preferably, the composition is essentially free of one or more selected from the group consisting of menthone, menthyl acetate, limonene, neomenthol, piperitone, pulegone, β - caryophyllene, β-caryophyllene-epoxide, α-pinene, β-pinene, germacrene D, 1,8-cineol, linalool, menthofurane, camphene and β-hexenyl phenylacetate. Even more preferably, the pharmaceutical composition is essentially free of menthone, menthyl acetate, limonene and neomenthol. Yet more preferably, the pharmaceutical composition is essentially free of menthone, menthyl acetate, limonene, neomenthol, piperitone, pulegone, β - caryophyllene, β-caryophyllene-epoxide, α-pinene, β-pinene, germacrene D, 1,8-cineol, linalool, menthofurane, camphene and β-hexenyl phenylacetate. It is also preferred that the pharmaceutical composition is

> essentially free of one or more preferably all compounds selected from the group consisting of menthone, menthyl acetate, limonene, neomenthol, piperitone, menthenone, isomenthone, pulegone, β -caryophyllene, β-caryophyllene-epoxide, α-pinene, β-pinene, germacrene D, 1,8-cineol, linalool, menthofurane, camphene and β-hexenyl phenylacetate. [emphasis added]

Claims 90-92 are based on the above passage.

The Examiner should recognize that the excluded menthone is a significant constituent of peppermint oil, as is menthyl acetate. Comparison of the above passage with the list of minor peppermint oil components, at page 9, lines 29-33, is also instructive.

New claim 87 recites that the purified menthol is at least 90% pure. At page 10, lines 1-5 the specification teaches

> Purified menthols may have been purified from a plant or it may have been synthesised chemically. Menthol purified from a plant is <u>preferably essentially free of any other compounds of said plant</u>. Menthol according to the invention is preferably levo-(-)-Menthol (also designated (-)-menthol. Useful pharmaceutical acceptable expients are described herein below. [emphasis added]

While there is no specific definition of "purified menthol", we believe it instructive to consider the discussion of "purified flavonoids" at page 10, lines 8-17:

> By the term "purified flavonoids" is meant one or more flavonoids essentially free of any other compounds. Hence, a composition of "purified flavonoids" comprises at least 90% flavonoid, preferably at least 95% flavonoid, more preferably at least 98% flavonoid, even more preferably aprroximately 100% flavonoid. A composition of "purified flavonoids" thus most preferably does not contain any other detectable compound. In particular, it is preferred that purified

> flavonoids are free of other compounds present in the composition from which they are purified. By way of example, if the flavonoid is purified from a plant extract, it is preferred that the purified flavonoids are essentially free of any other compounds present in the crude plant extract.

We believe that if "purified flavonoids" are defined as being at least 90% flavonoid, then, mutatis mutandis, "purified menthols" must be at least 90% menthol, absent express teachings to the contrary. The level of menthol in peppermint oil is substantially less than 90%.

Example 2 describes use of "pure Menthol (-) from Sigma". According to Sigma product sheets both of its menthol products are over 99% pure. (Exhibits 3 and 4.)

New claim 88 recites that the composition is in a form suitable for nasal administration. Basis is at page 31, line 14.

New claim 89 recites that the composition is in a form suitable for aerosol administration. Basis is at page 31, lines 22 to 24. New claim 90, dependent on 89, adds that the composition is provided in a pressurized pack which further comprises a propellant. Basis is at lines 26 to 29.

It should be noted that the term "essentially consists", which is used in claims 11, 12, 13, 86 and 92, is defined by P11, L1-2:

> By the term "essentially consists of" is meant that no other ingredients are detectable by commonly used detection techniques.

2. Election/Restriction (OA pp. 2-4)

PCT unity rules apply to this case. The Examiner has made a holding of a posteriori lack of unity, based on the prior art WO 02/09699, and restricted between the

compositions (claims 1-27) and the methods-of-use (claims 54-71, 74-78, 81-83).

In response to this requirement, applicant "prospectively" elected group I with traverse, see discussion at OA page 4 and page 3 of the September 20 election.

The requirement was and is traversed because the claims are in fact patentable over the art, for the reasons set forth in section 3 below. Consequently, the group II method claims should be rejoined in accordance with the PCT Administrative Instructions, Annex B, part 1, paragraph (e)(i), as well as MPEP 821.04.

3. Indefiniteness Issue (OA pp. 4-5)

The indefiniteness rejection (OA pages 4-5) of claims 2 and 4 is moot as those claims have been cancelled.

4. Prior Art Issue (OA pp. 5-6)

Claims 1-27 stand rejected as obvious over Berg et al., WO 02/09699. This rejection is respectfully traversed.

Claim 1 is directed to "A pharmaceutical composition comprising one or more purified flavonoids; and **purified menthol**; and pharmaceutically acceptable excipients." Claim 3 adds that it further contains a metal salt or complex, and claim 5 that the metal is zinc.

Berg is said to teach compositions comprising purified flavonoids and zinc metal complexes/salts, and optionally peppermint oil. The Examiner asserts that the "major constituent" of peppermint oil is menthol and holds that it is prima facie obvious to modify Berg's composition by replacing the peppermint oil with purified menthol.

4.1. Before addressing the examiner's legal arguments, we need to set the record straight regarding the menthol content of peppermint oil.

Applicant respectfully submits that peppermint oil, rather than consisting mainly of menthol, comprises a number of different components, and thus "purified menthol" may have different biological properties than peppermint oil.

The peppermint oil used in commerce as a flavor or fragrance is actually a byproduct of the production of pure menthol by steam distillation. It is the "dementholized" fraction which doesn't crystallize out when the distillate is cooled. See www.aurumindia.com/ereports/MenthoaOil.pdf .

Dewick, D.M (Medicinal Natural Products, 2nd. edition,2002 (West Sussex, Wiley,) teaches that peppermint oil consists of menthol (30-50%), Menthone (15-32%), Menthyl acetate(2-10%) and menthofuran (1-9%); content of oil: 1-3%. A copy of the reference is enclosed (exhibit 1).

Dewick's analysis is supported by a datasheet from the manufacturer of the peppermint oil which was used in the experiments described in the present patent application. The datasheet lists the following composition: Menthyl acetate: 2.8-10%; Menthol: 30-55%; Menthone: 14-32%; other substances (fatty oils and resinified essential oils and acidic matter, etc.) were within the EU-limits. A copy of the datasheet is enclosed (exhibit 2).

We are not aware of any authority which asserts that peppermint oil contains 90% or more menthol as required by claim 87, and exhibits 1 and 2 suggest that the menthol content is quite a bit lower than 90%.

4.2. The Examiner argues, in support of the finding of prima facie obviousness, that changing the level of purity of

the menthol is an obvious modification, and the mere optimization of a variable, and that the motivation would be to obtain a purer composition.

The instant claims, of course, are not to a purified menthol composition, but rather to the combination of the purified menthol with a purified flavonoid. It is therefore necessary to inquire into why Berg adds peppermint oil to his composition, and whether, in the context of the disclosed purpose of the peppermint oil, whether the art would have found it obvious to replace the peppermint oil with a purified menthol.

In Berg et al., peppermint oil is added to the pharmaceutical compositions merely for flavoring purposes (see p. 24, l. 1-6). Berg et al does not suggest that peppermint oil has any <u>therapeutic value</u> in relation to treatment of common cold. Consequently, Berg et al nowhere teaches that any components of peppermint oil, such as menthol, would have therapeutic value in treatment of common cold.

Nor does Berg suggest that the flavor of the composition would be improved if peppermint oil were replaced with purified menthol. Replacing peppermint oil with purified menthol would result in the loss of all of the lesser components which contribute to the overall taste of peppermint oil.

According to Maarse, Volatile Compounds in Foods and Beverages 470 (Exhibit 5), a literature review by Lawrence reported that "some of the minor constituents play an important role in the overall flavor/ordor profile" of peppermint oil from American Mentha piperita. By way of example:

aliphatic esters... fruity notes
aldehydes... green notes
trans-isopulegone (LVI) and (Z)-jasmone (LVII)... floral notes
aliphatic acids... mellowing notes
viridflorol (LVIII)... sweet notes

Additionally, the menthofuran (LIX) and mint lactone (LXI) contributed, together with the menthol (IV), to the "minty organoleptic quality".

Maarse also states (471) that Sakurai identified two new series of peppermint constituents one with a "faintly fruity, sweet aroma", and the other with "cinnamon-like, leafy-green, minty and spicy aromas". (Exhibit 5)

If the person of ordinary skill in the art was indeed trying to improve the flavor of the composition by replacing the peppermint oil with one of its purified constituents, it does not necessarily follow that the desired constituent would be the menthol. It could, instead, be the menthone, or even a more minor constituent of peppermint oil. Nowhere does Berg state that he is adding peppermint oil for the sake of its menthol content.

Nor would the person of ordinary skill in the art necessarily believe that it was necessary or desirable to go to the expense of purifying the menthol to the point at which it was 90% pure (claim 87) or "essentially free of components of peppermint oil other than menthol" (claim 86) or "essentially free of one or more selected from the group consisting of menthone, menthyl acetate, limonene and neomenthol" (claim 13) or "essentially free of other terpenes

than menthol" (claim 12), or the further compositions of claims 90-92.

In addition, replacing peppermint oil with purified menthol could have been thought undesirable in other ways. For example, Sturtz, Plant Patent 08645, LOW MENTHOL MINT PLANT MENTHA SPICATA L. `EROSPICATA` teaches that a peppermint-tasting essential oil with a low menthol content is desirable "because menthol is an alcohol that irritates nasal, oral and gastrointestinal epithelium." Sturtz offers, in its place, an oil high in menthone.

4.3. The Examiner also asserts that all that Applicants have done is to combine separate but well-known inventions (flavonoids, zinc metal complexes/salts, and menthol) which are performing the same function which they did when used separately, and which is yielding a predictable result.

The Examiner cites four Supreme Court cases: Great Atlantic & Pacific Tea Co. (1950), Anderson's-Black Rock (1969), Sakraida (1976), and KSR (2007).

In KSR, while it reversed the Federal Circuit decision,Indeed, it note that some Federal Circuit cases had applied TSM more flexibly than in the case which had drawn the high court's ire[1].

We respectfully urge that *KSR* did not overrule the Federal Circuit's "teaching-suggestion-motivation" test; it

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[1] 82 USQP2d at 1397, citing Dystar Textilfabriken GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1367, 80 USPQ2d 1641 (Fed. Cir. 2006) and Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1291, 80 USPQ2d 1001 (Fed. Cir. 2006). Commenters have drawn attention to In re Kahn, 441 F.3d 977 (Fed. Cir. 2006).

merely suggested that the particular Federal Circuit panel had, in that case, applied the TSM test in an overly rigid way. The Supreme Court conceded that "there is no necessary inconsistency between the idea underlying the TSM test and the Graham analysis". It said that the TSM test may provide "helpful insights", as long as it is not converted it into a "rigid and mandatory formula"[2]. It noted that it hadn't reviewed the TSM standard as more flexibly applied by the Federal Circuit in Dystar Textilfabriken GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1367, 80 USPQ2d 1641 (Fed. Cir. 2006) and Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1291, 80 USPQ2d 1001 (Fed. Cir. 2006).

Consequently, TSM can and should be applied here, provided that we avoid the errors noted by the Supreme Court: (1) not limiting the search for motivation to the problem which the patentee (applicant) was seeking to solve, (2) not limiting the search for combinable elements to those designed to solve the same problem, and (3) denigrating as "obvious to try" a search for a solution from among a small number of alternatives.

Under KSR there must still be a "reason to combine" the references, and the courts must also examine the result of the combination to see whether it exceeded expectations.

In A&P Tea, cited by the Examiner, the Supreme Court remarked, "Elements may, of course, especially in chemistry or electronics, take on some new quality or function from being brought into concert, but this is not a usual result of uniting elements old in mechanics."

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[2] 550 U.S. ___, 127 S. Ct. 1727, 82 USPQ2d 1385, 1396 (2007).

The present invention is drawn to a chemical composition and the menthol element has indeed taken on a new quality or function, displaying, in its combination with the flavonoid, an antiviral effect. In contrast, its known function in the cited prior art had been merely to enhance the flavor of an ingested composition.

Indeed, it is fair to characterize the result of the combination of purified menthol with purified flavonoid as being synergistic; no "synergistic result" was argued in the Anderson's Black Rock case mis-cited by the examiner as In re Anderson, see 163 USPQ at 674. In Sakraida, a "synergistic result" was suggested, but the Supreme Court decided that this was a mis-characterization, as each of the elements was "performing the same function it had been known to perform." Purified menthol has not previously been known to have an antiviral effect, whether alone or in combination with a purified flavonoid.

The antiviral effect contributed by the menthol was an unexpected and unpredictable one which supports a conclusion of nonobviousness, as further discussed below.

4.4. One technical problem solved by the present invention is to provide pharmaceutical compositions with enhanced efficacy for treatment of common cold. With respect to this purpose, the results provided by the claimed composition, incorporating a purified menthol, are unexpectedly superior to those provided by the peppermint oil-flavored composition of the Berg reference.

The Applicant wishes to draw the Examiner's attention to the experiments described in the present application (wide Examples, p. 33-38) wherein fundamental differences between

pure menthol and peppermint oil are disclosed, especially regarding biological properties in respect of virus replication and the HuIFN-alpha system:

1. Pure menthol is not toxic to the cells used in the experiments within a practical range (less than 0.04 weight %).

2. Pure menthol has a direct antiviral activity vs. rhinovirus in cell culture experiments. As demonstrated in Figures 2A and 2B cells treated with menthol (0.04%) were protected to a significantly higher degree (approx. 25%) compared to untreated cells (statistically significant) - cf. this patent appl., Example 2, p.34, l.25 - p.36, l.11.

3. Pure menthol is able to potentiate the human interferon-alpha system (interferon is produced by the host during the rhinovirus infection). This is demonstrated in Figures 1A and 1B, wherein an increased cell viability is observed for cells treated with menthol + interferon rather than just interferon - cf. Example 2, p.34,l.25 - p.36,l.11.

4. Dilutions of Peppermint oil (PPO) were shown to be rather toxic to the cells, the experiments yielding unpredictable results. Experiments analogous to those described above under point 2 with dilutions of PPO were thus unsuccessful. Meaningful results, however, were obtained when switching to the "volatile PPO technique" i.e. with PPO in a gaseous form (cf. example 3).

5. Peppermint oil (as vapor) increases the production of rhinovirus in cell culture experiments. The results in Figure 3A demonstrate that the presence of the volatile parts of PPO increases the amount of virus produced. In contrast to the virus control dose-response curve (HRV control, with no PPO), the virus dose-response curve with PPO is almost independent of the dilution of the virus.

6. Peppermint oil vapor depresses the human-alpha interferon system in cell culture experiments cf. the description in the Appl. p.37,l.24-p.38,l.3.

The Applicant further wishes to draw the Examiner's attention to the experiment (Example 4, page 38 l. 7 to page 42, l. 15) described in the present application wherein the efficacy of pure menthol versus peppermint oil in the treatment of common cold patients is disclosed.

As is apparent from Table 1, the over-all reduction in symptom score (SS) at day 3 corresponds to 90% reduction after treatment with purified Menthol+flavonoid. In contrast, the over-all reduction in symptom score after treatment with peppermint oil+flavonoid was merely 80% (see table 2).

The variation in SS between the groups treated with menthol- or PPO-lozenges was significantly smaller in the menthol-treated group (compare results of fig. 4E and 4D).

An additional advantage of the menthol-lozenges is that purified menthol is able to eliminate the metallic taste of the ZnGluconate present in the Zn-containing lozenges (cf. page 42, lines 9-10).

Accordingly, in contrast to peppermint oil, purified menthol has direct antiviral activity *in vitro* and is capable of potentiating the interferon alpha system. Thus use of purified menthol cannot be considered equivalent to use of peppermint oil, despite the fact that peppermint oil comprises menthol.

4.5. Since the menthol of peppermint oil was not known to have any antiviral effect, it would not have been expected to enhance the antiviral activity of the flavonoid-zinc composition, merely to improve its flavor.
Hence, the art would not have expected the applicants' purified menthol-flavonoid-zinc composition to be superior in antiviral activity to the comparable peppermint oil composition. The experimental results delineated in the specification shows that it is indeed superior, and we have already explained why that superiority would have been considered unexpected.

Anderson's Black Rock and Sakraida, on which the examiner relies, stated that if a combination is synergistic, that is, the effect of the combination is greater than the predictable additive effect of its components, the combination is patentable. Since the menthol in the prior art composition was not known to have any antiviral effect, the predictable additive effect of the claimed composition would have been equal to the effect of the flavonoid/zinc combination alone. The increased effect observed by applicants is therefore an example of patentable synergy.

The Federal Circuit has repeatedly held that a case of prima facie obviousness can be rebutted by a showing of unexpectedly superior results. See, e.g., In re Sernaker, 217

USPQ 1, 5 (Fed. Cir. 1983); In re Chupp, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987); Kao Corp. v. Unilever US, Inc., 78 USPQ2d 1257 (Fed. Cir. 2006). Such results have been disclosed in the specification.

4.6. Additionally, the courts have recognized that a long-felt but unsatisfied need, which was at last satisfied by the claimed invention, is an indication of non-obviousness.

That there is a long-felt but not fully satisfied need for agents which, rather than alleviate symptoms, attack the rhinoviral cause of the common cold, can hardly be doubted. See discussion in Berg, pages 1-6.

Eccles (Ref. AZ) teaches that menthol was already used, by 1890, in the treatment of "diseases of the upper air passages", and that it has been widely used "for the relief of common cold symptoms such as nasal congestion and cough." Despite this long usage, it does not appear that it was ever suggested that menthol might have an actual antiviral effect, and indeed Eccles notes that "there is little hard scientific evidence to support any nasal decongestant or antitussive activity."

Fisitin and flavone are examples of flavonoids. According to the Merck Index, the earliest references for the flavonoid fisetin are Chevreul, Lecons chim appl a la teint (1833) and J SChmid, Ber. 19, 1734 (1886), and the earliest references for the flavonoid flavone are Feuerstein, Kostanecki, Ber. 31, 1757(1898) and Kostanecki, Tambor, Ber. 33, 330 (1900). Thus, flavonoids have been known since at least 1833!

Nonetheless, as of applicants' Danish priority date (2002), there still had not been any teaching in the art that the combination of a purified menthol and a purified flavonoid would be useful in the treatment of the common cold.

In conclusion, a person skilled in the art seeking to provide improved pharmaceutical compositions for treatment of common cold would therefore not have been led to believe by Berg et al. that peppermint oil, or any components thereof, provide any advantageous effect other than improved flavor. In particular, said skilled person could not, based on Berg et al, have reached the conclusion that pharmaceutical compositions comprising purified menthol in combination with flavonoids are superior in antiviral activity over similar compositions comprising peppermint oil in combination with flavonoids. The superiority which they in fact manifested was thus unexpected and deserving of patent protection.

The examiner is respectfully requested to acknowledge the non-obviousness of claim 1 and claims dependent thereon.

4.7. Berg teaches an oral composition in which peppermint oil is used as a flavoring agent. Claim 88 is directed to a composition which is in a form suitable for nasal administration. While Berg generically teaches nasal administration of flavonoid/zinc compositions, Berg does not teach including a flavoring agent in such compositions.

It would not be rational to incorporate a flavoring agent, such as peppermint oil, into such a composition, and therefore it would not occur to the art to provide a

composition for nasal administration which includes purified menthol as a substitute flavor.

Claim 88 recites that the composition is in a form suitable for aerosol administration. Claim 89 adds that the composition is provided in a pressurized pack which further comprises a propellant. It would not be rational to include a flavoring agent in such compositions.

5. Miscellaneous

Counsel respectfully request the examiner's advice as to whether, and how, to correct the use of the term "flagrant" in the specification.

The specification uses "flagrant" at page 5, line 33 to refer to the peppermint oil in the Berg reference; this was use as a flavor. It is also used at page 6, lines 3 and 7; page 9, lines 13, 16-17.

There does appear to be some current acceptance of the term "flagrant" to refer to a flavor in British English, see (WO/1999/021432) FLAVOURING MATERIALS FOR USE IN TEA CONTAINING BEVERAGES ("The present invention relates to the use of natural and synthetically prepared **flagrant** materials which also act as antimicrobials in aqueous based beverages containing tea solids.") And the Oxford English Dictionary, under "flagrant", meaning 6, states that it is an obsolete synonym for "fragrant".

Counsel's question is whether the term should be left as is, or replaced by "flavor", by "fragrance" or by "fragrance or flavor". The appropriate replacement may vary from occurrence to occurrence.

In the case of the discussion of Berg, it is apparent that the intended meaning was as a flavor. Berg expressly

teaches use of flavors, but not of fragrances, see page 23; line 27, and the peppermint oil is taught for use in an oral composition, see page 24, lines 1-6.

5.2. References BC and BD from the December 16, 2005 IDS were not considered because these references were "not translated". Applicants are not required to provide an English translation unless a translation is already in their possession or control, or readily available to applicants. See 37 CFR 1.99(a)(3)(ii). No such translation is available, i.e., applicants would have to order and pay for such a translation. All that is otherwise required is a "concise explanation of the relevance" of the reference, see (3)(i). Reference BC includes an internal abstract which is deemed to satisfy the "concise explanation" requirement. As to reference BD, we enclose an abstract prepared by the applicants' European attorney.

Respectfully submitted,

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Enclosures
-Exhibits 1-5
-Abstract for BD

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